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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/211,297	12/14/1998	WILLIAM J. BOYLE	A-451-F	7253

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/211,297	BOYLE, WILLIAM J.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 August 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *13 August 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *82-92*.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance because: Claims 82-92 stand rejected under 35 USC 112, first paragraph, enablement. The rejections are maintained for reason of record. Applicant discusses the Jakobovits and Bruggemann references. Applicant argues that the Examiner has ignored the positive results reported with transgenic mice and instead emphasizes the drawbacks regarding human antibody production in mice. Applicant states that Jakobovits refers to the use of CD4 and IgE antibody, both proteins, to elicit human antibodies in transgenic mice. Applicant concludes by stating that one skilled in the art following the Jakobovits and Bruggemann references as examples could apply the teachings therein to the generation of other transgenic animals. Applicant maintains that there is nothing in the references to suggest otherwise and no reason why one skilled in the art could not do so.

Applicant's arguments have been fully considered but not considered persuasive. The Examiner has not ignored the results reported with transgenic mice. The Examiner stated that Jakobovits teaches that human Ig transgenic mice are capable of mounting an antigen-specific human antibody response upon immunization with model antigens, such as tetanus toxic C and human antigens such as CD4 and IgE (see previous Office Action, 11 February 2004, page 4, last pargraph-page 5). The antigens used by Bruggemann (Table 2, page 396) were the same model antigens (tetanus toxic C, human CD4). Regarding Table 2, (as pointed out by Applicant), Bruggemann states, "even when an IgH minilocus is expressed in a mouse strain that has its own functional endogenous loci, it has been possible, following antigen challenge, to obtain hybridomas in which the minilocus contributes antigen binding specificity". "However, in such mice, the majority of the antigen specific hybridomas use endogenous mouse Ig chains to form the antigen-specific antibody". Bruggemann states, "the isolation of hybridomas in which antigen specificity is contributed by the transloci is therefore greatly facilitated when the transgenic mice have been crossed into a knockout mouse background with silenced endogenous Ig loci". "In such cases, mice carrying transgenic miniloci or YAC-based transloci have been found to give reasonable antibody responses to a variety of antigens".

Mouse monoclonal antibody production is vastly different from human antibody production. The specification, as originally filed, fails to provide sufficient guidance regarding the expression of human antibodies directed against osteoprotegerin binding protein from transgenic non-human animals and fails to disclose examples demonstrating enablement of the recited claims. The specification does not teach how to make a transgenic animal that produces human antibodies. The specification fails to teach various methods such as Ig rearrangement (using minoloci, YACs) or crossing human Ig transloci into mice wherein the endogenous Ig loci has been silenced (knock-out mice). The specification fails to teach the steps for making human antibodies by immunizing a transgenic animal. There is a high level of unpredictability in the art regarding the instant invention. As was stated in the last Office Action, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lack of a working example is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. Bruggemann states, "however, while the results are certainly very encouraging, the full extent of the repertoires and affinities that can be obtained from the transgenic animals has not been completely explored"." It could still be that some of the mice have holes in their repertoires, making it difficult to isolate very high affinity antibodies against certain individual epitopes".

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER